Serial No.: 09/705,579

REMARKS

Claims 42, 44, 55, 63 and 65 are cancelled herein without prejudice or disclaimer, in order to expedite prosecution. Claim 70 to humanized forms of 4D5 (e.g. Trastuzumab) is added with support therefor found on at least page 17, line 29. New claim 71 is supported in claim 69 and page 17, line 29, for example. In that the amendments do not introduce new matter, entry thereof is respectfully requested.

The sole remaining rejection in the case is an obviousness rejection based on Hudziak et al. (US Patent No. 5,720,954) in view of Pauwels et al. *J. Pharm. Pharmacol.* 47(10): 870-875 (1995).

Applicants have provided evidence including Burstein et al. (2001), Filipovich et al. (2002), and "Exhibit A" summarizing data from Pegram et al. (1999), Pegram et al. (2000), Slamon and Pegram (2001), and Hirsch et al. (2002). These data demonstrated that, whereas the HER2 antibody and **Vinblastine** referenced in column 6, line 64 of the primary reference had an additive Combination Index (CI) score of **1.09**, the HER2 antibody and **Vinorelbine** combination recited in the claims of the present application had a *synergistic* CI of **0.34**. In addition, of the 16 different chemotherapies referenced in Exhibit A, Vinorelbine - the chemotherapeutic agent recited in the claims of the above application - had the **best CI**, 0.34, same as that achieved with the combination of Docetaxel *plus* Carboplatin.

The Examiner does not dispute the above unexpected results, but contends that this objective evidence of nonobviousness is not "commensurate in scope" with the claims "drawn to the treatment of a broad array of cancer or tumors (i.e. those that overexpress or have activated ErbB2." The Examiner does agree that the references relied upon do "indicate synergistic effects of the anti-HER2 antibody in combination with vinorelbine *for the treatment of breast cancer*" (emphasis added). See Advisory Action mailed 02/09/2006.

Purely in the interests of expediting prosecution, and without acquiescing in the rejection, Applicants have cancelled claims 42, 44, 55, 63 and 65, such that claim 69 drawn to "treating breast cancer" remains. Claims 70 and 71, likewise directed to breast cancer therapy, are added. The Examiner indicates

in the 02/09/2006 Advisory Action that claim 69 is commensurate in scope with the objective evidence of nonobviousness. However, in the 03/08/2006 interview, the Examiner indicated that the Exhibit filed 12/16/2005 was not commensurate in scope with claims drawn to a genus of HER2 antibodies, that "while the exhibits show 4D5 antibodies or humanized forms of the 4D5 (Trastuzumab), it does not provide for other antibodies that bind to the same epitope bound by 4D5."

Applicants submit that claim 69, referencing breast cancer therapy with an "anti-ErbB2 antibody which binds to an ErbB2 epitope bound by antibody 4D5" and Vinorelbine, is commensurate in scope with the evidence of nonobviousness. In particular, the genus of antibodies that bind to the 4D5 epitope was well defined and characterized at the time of filing the above application in 1996. The specification refers to the "epitope 4D5" at page 13, lines 1-7. Antibodies that bind to the 4D5 epitope can be screened for using a routine cross-blocking assay such as that described in a laboratory manual, or can be identified by epitope mapping. Epitope mapping studies are illustrated in Fig. 13. Antibody 4D5 binds residues in the "Domain 4" region of the HER2 extracellular domain, adjacent to the transmembrane domain, in particular residue(s) in the region from about residue 561 to about residue 625. Antibody 3H4 is another anti-ErbB2 antibody which binds to the 4D5 epitope as determined by epitope mapping studies (see Fig. 13 of the present application), and cross-blocking studies (see Table 1 on page 1555 of Fendly et al. Cancer Research 50: 1550-1558 (1990), of record, where antibody 3H4 is shown to block binding of antibody 4D5 to HER2). Like antibody 4D5, antibody 3H4 inhibits proliferation of HER2 overexpressing-breast cancer cells (see Fig. 3 of US Patent No. 5,720,954, Hudziak et al., relied upon in the Section 103 rejection). Applicants submit that it is readily apparent that those skilled in the art could make antibodies, like 4D5, which bound to its epitope, and were effective for breast cancer therapy, based on the disclosure of the present application, as well as the level of skill in the art at the time of filing the above application. Moreover, Applicants submit that such antibodies, when combined with Vinorelbine, would demonstrate the unexpected results discussed above, through exerting their therapeutic effect upon binding to the 4D5 epitope.

Aside from the evidence of nonobviousness discussed above, Applicants further submit that the presently claimed invention is patentable over the art in that

the primary reference does not disclose Vinorelbine as claimed herein, and the secondary reference, Pauwels et al., while disclosing Vinorelbine, provides absolutely no motivation to combine it with a HER2 antibody. Hence, Applicants contend that a *prima facie* case of obviousness has not been made out. While the Examiner has opined that "the vinca alkaloid family *appears* to rely on the same mechanism of action" (emphasis added) and that, therefore, "one of ordinary skill in the art would expect that the use of any vinca alkaloid drug would have the same effect on the treatment of malignant disease" (Office Action dated 06/15/2005, page 3), this is contradicted by the scientific data. See, in particular, Exhibit A which shows that the HER2 antibody plus Vinblastine combination had a CI of 1.09 compared to a CI of 0.34 for the HER2 antibody plus Vinorelbine combination claimed herein. Moreover, Applicants have provided evidence to demonstrate that Vinorelbine is structurally and functionally distinct from Vinblastine (see internet excerpt entitled "Pharmacology of Vinblastine, Vincristine, Vindesine and Vinorelbine" attached to the 03/01/2004 amendment).

Reconsideration and withdrawal of the Section 103 rejection is respectfully requested.

Applicants refer now to the terminal disclaimer (TD) over US Patent No. 5,720,954 filed 03/01/2004. As noted then, the TD was filed purely in order to expedite prosecution, and without acquiescing in the rejection. Applicants provide herewith a petition under 37 CFR 1.182 requesting withdrawal of the recorded TD. Applicants submit that the TD over the '954 patent is unnecessary in view of the evidence provided to date demonstrating unexpected results associated with the presently claimed method.

Applicants believe this application is now in condition for allowance and look forward to early notification to that effect. If, however, issues remain, the Examiner is invited to call the undersigned to discuss any such issues, and thereby expedite prosecution.

Respectfully submitted,
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